

REMARKS

In the Office Action dated April 3, 2008, claims 38 and 42-47 are pending and under consideration. Claims 38, 42-43 and 47 are rejected under 35 U.S.C. §102(b) as anticipated by Richardson et al. (*Environ Mutagenesis* 1981, 3:545-553) (hereinafter "Richardson"). Claims 44-46 are rejected under 35 U.S.C. §103(a) as unpatentable over Richardson in view of Nikiforov et al. (U.S. Patent 5,610,287) (hereinafter "Nikiforov").

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

Independent claims 38 and 47 have been amended to include in the claimed method, an active step of "obtaining an aquatic, terrestrial, gaseous or industrial environmental sample". Support for this language is found in the specification, e.g., on page 7, lines 28-31. Claims 38 and 47 have also been amended to clarify that "metal ions" are being detected as toxicant by the claimed method, as supported by the specification, e.g., at page 10, lines 12-13. In addition, claim 47 further delineates that metal ions "at toxic levels" are being detected. Support for the language of "toxic levels" is found in the specification, e.g., page 7, lines 18-26.

No new matter is introduced by the foregoing amendments.

Rejection – 35 U.S.C. §102(b)

Claims 38, 42-43 and 47 are rejected under 35 U.S.C. §102(b) as anticipated by Richardson. According to the Examiner, Richardson teaches a method of detecting environmental mutagens and carcinogens in the environment, including Pb⁺², Zn⁺², Cd⁺², Fe⁺² and Pt⁺² (See Abstract; Figure 1 and Table II). Richardson allegedly teaches contacting the

samples containing the environmental toxicant ions with nucleic acid molecules intercalated with a fluorescent dye, and detecting the dissociating of the binding between the nucleic acid molecules and said fluorescent dye, wherein said dissociation of the binding is indicative of the presence of the environmental toxicant. The Examiner states that the assay taught by Richardson can detect these environmental metal ions in the range of micromolar amounts.

Applicants respectfully submit that Richardson relates to the measurement of the concentration of metal ion in a laboratory-contrived solution. In contrast, the amended claims are directed to a method for detection of metal ions in an environmental sample. In this regard, the claims have been amended such that the claimed method includes a step of "obtaining an aquatic, terrestrial, gaseous or industrial environmental sample". Applicants respectfully submit that those skilled in the art would understand that an environmental sample is a small amount of e.g. water, soil, air, gas, that can be collected to measure contamination in the environment at a specific location. This interpretation of environmental sample is in line with the glossary definitions published by both the United States Environmental Protection Agency and The Agency for Toxic Substances and Disease Registry, copies of which are attached hereto as **Exhibits 1-2**. Further, in Richardson, each metal ion was analyzed independently, i.e., all the assays measured one metal ion at a time. There is no discussion in the reference on how to detect in a single assay, metal ions in an environmental sample, which typically contains more than one metal ion, in contrast to the presently claimed method.

Applicants therefore respectfully submit that Richardson does not teach detection of metal ions in an environmental sample, as presently claimed. Therefore, the §102(b) rejection based on Richardson is overcome and withdrawal thereof is respectfully requested.

Rejection – 35 U.S.C. §103(a)

Claims 44-46 are rejected under 35 U.S.C. §103(a) as unpatentable over Richardson in view of Nikiforov. The Examiner admits that Richardson does not explicitly teach immobilizing DNA on a solid substrate. However, Nikiforov allegedly teaches immobilizing DNA molecules on the substrate of a 96-well microtiter plate to improve analysis in a rapid, convenient and inexpensive manner. Therefore, the Examiner concludes that it would have been obvious to one ordinary skilled in the art at the time the invention was made to immobilize DNA molecules on the substrate of a 96-well microtiter, as taught by Nikiforov, in the method disclosed by Richardson and arrive at the claimed invention.

"To establish a prima facie case of obviousness of a claimed invention all the claimed limitations must be taught or suggested by the prior art". *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 44, 496 (CCPA 1970). Applicants respectfully submit that the cited references fail to teach or suggest detecting metal ions in an environmental sample, as presently claimed. In particular, there is no teaching or suggestion in either reference for obtaining an aquatic, terrestrial, gaseous or industrial environmental sample and contacting such sample with appropriate reagent for detection of metal ions, as presently claimed. Therefore, Applicants respectfully submit that the Examiner has not made out a case of *prima facie* obviousness.

Furthermore, Applicants respectfully submit that the present invention provides a rapid and accurate assay for measuring heavy metal toxicants in environmental samples. The results achieved by the present invention are unexpected to those skilled in the art. In support of this position, Applicants provide herewith a Declaration of Professor Cristobal Guillermo dos Remedios, a co-inventor of the present application (**Exhibit 3**).

As Professor dos Remedios stated in the Declaration, Paragraph 7, previously known methods include live whole organism or cell-based assays where the toxicity of an environmental

sample is determined by assessing the effect of sample exposure on the viability and/or phenotype of the organism/cell. These prior art methods are described in the references listed in the Information Disclosure Statement and PTO Form 1449, which are being electronically filed on August 4, 2008.

Professor dos Remedios further explained in the Declaration, Paragraph 8, these previously known assays, unlike molecular assays, were thought to best reflect the overall toxicity of an environmental sample because cellular defenses such as membrane barriers and cell receptors remained intact. By contrast, any molecule-based system, e.g., a nucleic acid based system, was widely considered incapable of providing a relevant or accurate measurement of toxicity for the reasons further discussed in the Declaration (see Paragraphs 9-10).

Specifically, multiple metals, which may be present in an environmental sample, do not necessarily merely have an additive toxic effect. The presence of one metal often has either a synergistic or an antagonistic effect on the activity of another metal in the sample, and *vice-versa*. This phenomenon affects the overall toxicity of the sample. For example, if Metal X and Metal Y each alone cause 1 arbitrary unit of toxicity, the additive effect would result in about 2 units, a synergistic effect would result in >2 units, and an antagonistic effect would result in <2 units.

Professor dos Remedios stated in the Declaration that the prevailing view in the art around the time of the conception of the present invention was that synergistic or antagonistic effects of multiple metal toxicants could only be measured with live whole organism or cell-based assay systems. Molecular assay systems, e.g. "naked" nucleic acid based systems, were thought not to be useful for this purpose due to the lack of *inter alia*, cellular machinery (e.g. enzymes), cell/organelle membranes and associated adsorption sites, intracellular and trans-membrane import/export mechanisms and intracellular and membrane-bound receptor

molecules. Up until the conception of the present invention and its reduction to practice, a molecular assay system would have been expected by the person skilled in the art to only be capable of measuring an additive effect. The instant inventors, however, have unexpectedly shown that a naked nucleic acid based assay is able to detect synergy and antagonism in mixtures of metals (see Paragraph 10 of the Declaration).

Accordingly, Applicants respectfully submit not only the cited prior art references do not teach or suggest the claimed invention, the claimed invention also provides a rapid and accurate means for measuring the toxicity of an environmental sample containing multiple heavy metal toxicants – a result that is unexpected to those skilled in the art. Therefore, Applicants respectfully submit that the presently claimed invention would not have been obvious to those skilled in the art. The §103(a) rejection based on Richardson and Nikiforov is overcome and withdrawal thereof is respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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